Exhibit 65

USP Education

Impurities in Drug Products and Drug Substances - A USP Approach

Ravi Ravichandran, Ph.D.
Principal Scientific Liaison

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Shankari Shivaprasad, Ph.D.

USP Affiliation: USP Employee
Title: Senior Scientific Liaison
Education: Ph.D. in Organic Chemistry, Bangalore University, India

Dr. Shivaprasad is currently a Senior Scientific Liaison at USP with responsibility for the development of documentary standards (monographs) for small molecular weight medicines intended for the United States Pharmacopeia. She provides support to the Chemical Medicines 1 Expert Committee.

Prior to Joining USP, Dr. Shivaprasad was a Principal Scientist at Lancaster Laboratories, Lancaster PA, with responsibility for analytical method development, method validation, documenting work as required for GMP compliance, produce writing/reviewing reports and collaboration with Lancaster project reviews with various Laboratories clients. Shankari played a key role in establishing the mass spectrometry facility for bio-analytical method development and validation of large molecules (biologics), under cGMP regulation.

Dr. Shivaprasad also held various positions at other biotech companies in the areas of research and development, mainly on peptide antibiotics and protein aggregation related to Alzheimer's disease.

Dr. Shivaprasad received her Ph.D. in Organic Chemistry from Bangalore University, India, and had subsequent postdoctoral appointments at the University of Zurich, Switzerland, and the University of Tennessee, Knoxville, USA. She has more than 20 publications including review articles in peer-reviewed journals and has also written book chapters.

Ravi Ravichandran, Ph.D.

USP Affiliation: USP Employee since 2004
Title: Principal Scientific Liaison
Education: Ph.D. in Analytical Chemistry, University of Louisville, Louisville, KY

Dr. Ravichandran has been employed at USP since 2004. In this role as a scientific liaison, he has been supporting the Expert Committees involved in the introduction and revision of documentary standards for psychiatric drugs, inhalation products and radioactive drugs and contrast imaging agents. He provides support to the Chemical Medicines four Expert Committees. Ravi has over 35 years of experience in both industry and government.

Dr. Ravichandran's industrial experience includes several years in the diagnostics and pharmaceutical industry where he gained experience in analytical methods development for both raw materials and finished product characterization, methods and technology transfer to manufacturing sites, and QC laboratory management. Dr. Ravichandran received his Ph.D. in Analytical Chemistry from the University of Louisville, Louisville, KY. He had a subsequent postdoctoral appointment at the University of Georgia, where he worked with Dr. L.B (Buck) Rogers in the area of separations. He has several publications including review articles in peer-reviewed journals and has also written book chapters. In 1999/2000, Ravi served as the President of the Minnesota Chromatography Forum. He is actively involved in Washington Chromatography Discussion Group in MD.

Contents

Pharmaceutical Industry - History

1668	• Merck – Germany • Originated as a Pharmacy
1715	• Beecham (now GSK) • First Patented medicine in 1842
1849	• Pfizer – Started as Fine Chemicals • Expanded to provide medicines for Union war effort (US Civil War 1860-1865)
1858	• BMS – Edward Robinson Squibb – A US naval Doctor started a Laboratory – today's BMS.
1876	• Eli Lilly – Colonel Eli Lilly served in the US Army Set up Pharmaceutical Industry
1930	• Beginning of Concept of purity with the invention of Insulin and Penicillin – First two medicines that established the " Modern Pharmaceutical Industry "
19th Century	• Nature of the Industry is highly unregulated

Ref: Pharmaphorum Article, Sep 2010

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Thalidomide Scandal

"The Thalidomide scandal of 1961 prompted an increase in the regulation and testing of drugs before licensing…" **

- In the early 1950s the drug thalidomide was introduced as a sedative prescribed for nausea and insomnia in pregnant women.
- Found to cause severe birth defects in children whose mothers had taken it.
- FDA instituted a recall of Thalidomide and banned its use.
- As a result, the FDA established more stringent pre-market testing of drug safety and efficacy – but the system is not foolproof.
- Thalidomide is now approved for treating leprosy (1998)

*** Ref: Pharmaphorum Sep 2010*

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Contents

Drug Recalls

Recalls are action taken by a manufacturer to remove the product from the market

FDA updates Recall and market withdrawal information regularly

Recalls due to

- Visible Particulate matter in injectables
- Lack of Sterility Assurance
- Elevated impurity levels observed during stability
- Presence of undeclared drug ingredients
- Contamination
- Adulteration
- Container closure non-integrity
- Mold contamination

Recalls - Elevated Impurity Levels

- March 1, 2016
- **Sagent Pharmaceuticals Initiates a Nationwide Voluntary Recall of Fluconazole Injection, USP, (in 0.9% Sodium Chloride) 200mg per 100ml Due to the Discovery of an Out of Specification Impurity Result Detected During Routine Quality Testing of Stability Samples at the 18-Month Interval**
- More information https://www.fda.gov/safety/recalls/ucm489303.htm.

FDA Recalls, Market Withdrawals, & Safety Alerts http://www.fda.gov/Safety/Recalls/default.htm

Recalls - Elevated Impurity Levels

Recall of ARBs

- Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan
- https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan
  - FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities
  - The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products.
  - https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
  - USP is working with FDA to decide the path forward to help all the manufacturers

Tryptophan- Dietary Supplement

A poisonous substance in a GM food supplement killed 37 persons, and sickened over 60,000 patients.

Use of tryptophan as a dietary supplement discontinued in 1990.

- Tryptophan is a natural amino acid found in high protein rich foods and milk.
- Showa Denko had been producing tryptophan by fermentation for many years without any incident.
- Decided to use genetic engineered bacteria to accelerate and increase the efficiency of tryptophan production. No additional safety testing.
- More than 60 different impurities were identified in the L-tryptophan lots associated with the toxic effects.
- EBT (1,1'-ethylidene-bis-L-tryptophan) and MTCA (1-methyl-1,2,3,4-tetrahydro-beta-carboline-3-carboxylic acid) were implicated as being toxic.

***Published January 6, 2007. by PSRAST (**Physicians and Scientists for Responsible Application of Science and Technology A Global Network** - Last updated June 9, 2013.*

Other Recalls

- Leachables
  - (July 8, 2010) – McNeil Consumer Healthcare, Division of McNEIL-PPC, Inc.- recalled 21 lots of over-the-counter medicines because of consumer complaints of a musty or moldy odor.
  - Complaint linked to the presence of trace amounts of a chemical called 2,4,6-tribromoanisole (TBA).

FDA Recalls, Market Withdrawals, & Safety Alerts http://www.fda.gov/Safety/Recalls/default.htm

Other Recalls

- Contamination
  - West-Ward Pharmaceuticals Inc... recalled all lots of Ondansetron in 5% Dextrose Injection, supplied in 32mg/50mL Single-Use Plastic Bag Containers and Metronidazole Injection 500mg/100mL USP in Flexible IV Plastic Bag Containers.

Floating matter and non-sterility of Ondansetron and Metronidazole observed. (Manufactured by Claris Lifesciences)

Other Recalls

- Adulteration
  - Serious adverse reactions and deaths were reported for products containing Heparin Sodium USP.
  - FDA found that some of the adverse reactions and deaths may have been the result of heparin-like contaminants found in some of the recalled lots.

"Substandard" Medicines

- "One-Third of Antimalarial Medicines Sampled in Three African Nations Found to be Substandard in Large-Scale USP-WHO Study"
- *"'Substandard' medicines are those that do not meet the quality specifications set for them, primarily because they do not contain the correct amount of the active ingredient(s), do not dissolve properly in the body, or include unacceptable levels of potentially harmful impurities."*

"The Standard", USP, Spring 2010

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Contents

Definitions

- What are impurities?
- What is a degradation product?
- What is an impurity profile?
- What are concomitant Components?
- What are Foreign Substances / Extraneous impurities?

What are Impurities?

- **Impurity**
  - Drug Substance - Any component of a drug substance (DS) that is not the chemical entity defined as the drug substance.
    - Examples: Starting materials and by-products from DS Synthesis
  - Drug Product - Any component of a drug substance (DP) that is not the drug substance or an excipient in the DP.
    - Examples: Starting materials and by-products from DS Synthesis Components resulting from the DS and Excipient interaction.

What is a Degradation Product?

- **Degradation Product**
  - An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container–closure system.
    - Examples:
    - Salicylic acid in Aspirin (Acetyl Salicylic acid)
    - 4-Aminophenol in Acetaminophen
    - Memantine Lactose adduct in Memantine HCl Tablets
    - Cidofovir Uracil analog in Cidofovir

What is Impurity Profile?

- **Impurity Profile**
  - A description of the identified and unidentified impurities present in a drug substance or a drug product
  - Example:
    - Impurities listed in the monographs of pharmacopeia
    - List of potential Impurities / degradation products listed in the Standard Test Procedures of DS / DP.

What is Degradation Profile?

- **Degradation Profile**
  - A description of the degradation products observed in the drug substance or drug product.
  - Example
    - Zolmitriptan, Zolmitriptan Tablets, Zolmitriptan Orally Disintegrating Tablets and Zolmitriptan Nasal spray

Zolmitriptan and Dosage Forms Comparison

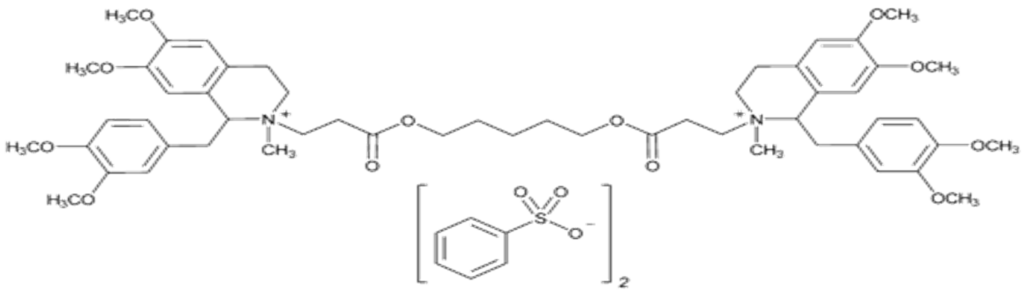
Name	API	Tablets	Orally Disintegrating Tablets	Nasal Spray
Zolmitriptan related compound B	0.2	NA	NA	NA
Zolmitriptan related compound E	0.2	0.6	0.6	NA
Zolmitriptan related compound F	1.2	NA	NA	NA
Zolmitriptan related compound G	0.1	0.2	0.2	NA
Zolmitriptan hydroxy ketone analog	NA	NA	NA	0.6
Zolmitriptan pyrrolo analog quaternary salt	NA	NA	NA	1.3
Zolmitriptan hydroxymethyl quaternary salt	NA	NA	NA	0.4
Zolmitriptan methylene dimer	NA	NA	NA	0.3
Any individual unspecified impurity	0.1	0.2	0.2	0.2
Total	0.5	1.5.	1.5	2.5

Other Possible Definitions

- Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the drug substance specification. A specified impurity can be either
  - Specified identified impurity
  - Specified unidentified impurity
- Unspecified impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the drug substance specification.
- Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image.
  - Example: Zolmitriptan and Zolmitriptan R-isomer

What are Concomitant Components?

- **Concomitant Components:**
  - Not necessarily impurities
    - Geometric and optical isomers (or racemates) of the drug substances and antibiotics that are mixtures.
    - Example: Atracurium Besylate



Atracurium Besylate

Definition –

- Atracurium Besylate contains NLT 96.0% and NMT 102.0% of $C_{65}H_{82}N_2O_{18}S_2$, calculated on the anhydrous basis. It contains
  - NLT 5.0% and NMT 6.5% of the trans-trans isomer, NLT 34.5% and NMT 38.5% of the cis-trans isomer, and NLT 55.0% and NMT 60.0% of the cis-cis isomer.

NOTE

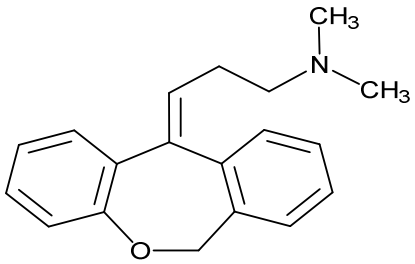
- trans-trans isomer, cis-trans isomer, or cis-cis isomer are not listed as impurities

What are Concomitant Components?

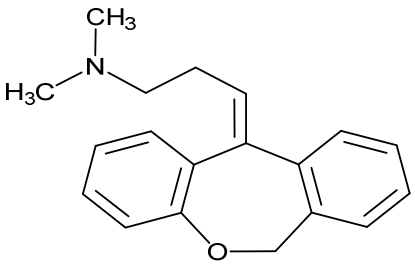
Doxepin Hydrochloride (*E*- and *Z*- Isomers)

Doxepin Hydrochloride, an (*E*) and (*Z*) geometric isomer mixture, contains the equivalent of NLT 98.0% and NMT 102.0% of doxepin hydrochloride ($C_{19}H_{21}NO \cdot HCl$), calculated on the dried basis.

It contains NLT 13.6% and NMT 18.1% of the (*Z*)-isomer, and NLT 81.4% and NMT 88.2% of the (*E*)-isomer.



• HCl



• HCl

What are Extraneous Contaminants?

- **Extraneous Contaminants (Foreign Substances)**
  - An impurity arising from any source extraneous to the manufacturing process
    - Introduced by contamination or adulteration.
    - Cannot be anticipated when monograph tests and assays are selected.
    - Allowance may be made in USP for the detection of these by non-compendial methods.
    - Manufacturers may have to evaluate for the presence of extraneous contaminants

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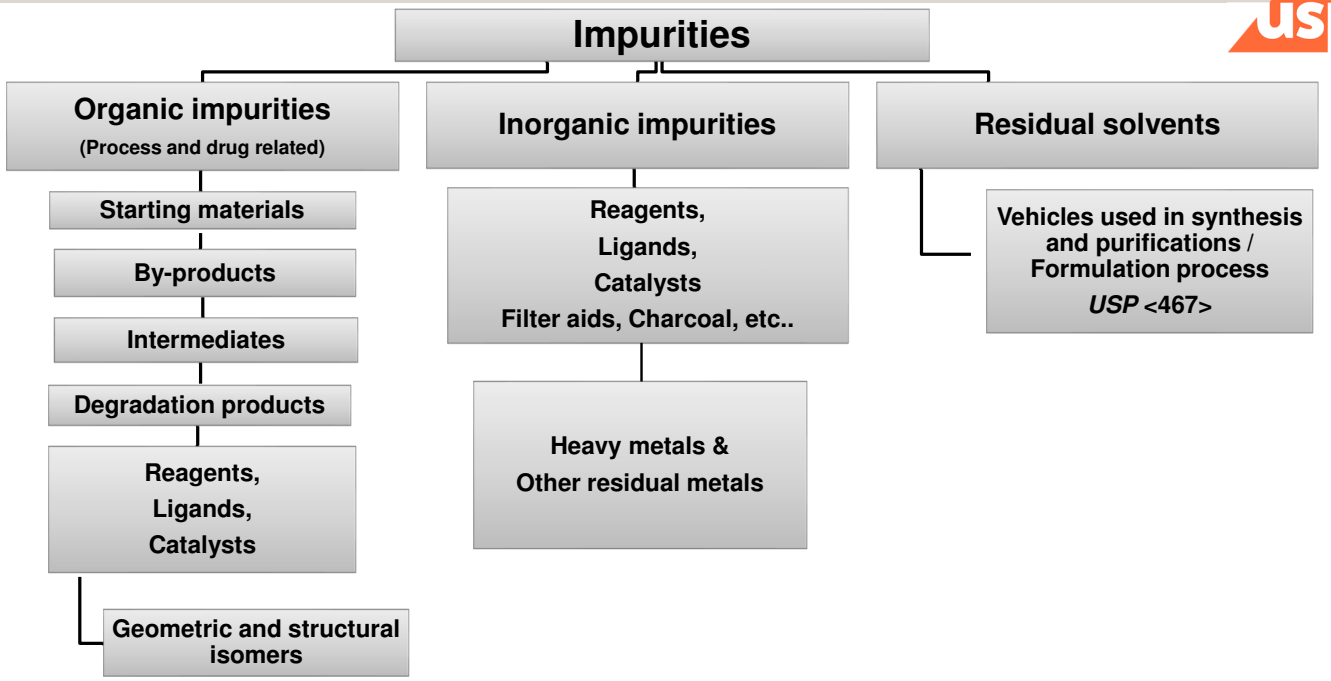
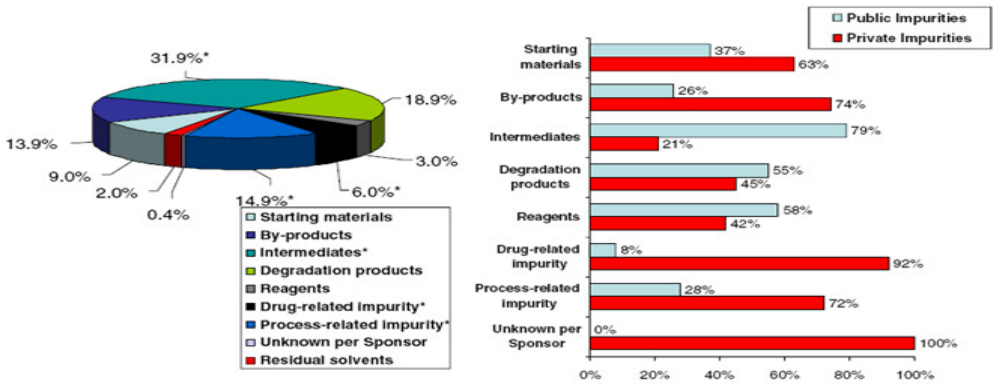
Classification of Impurities – DS and DP



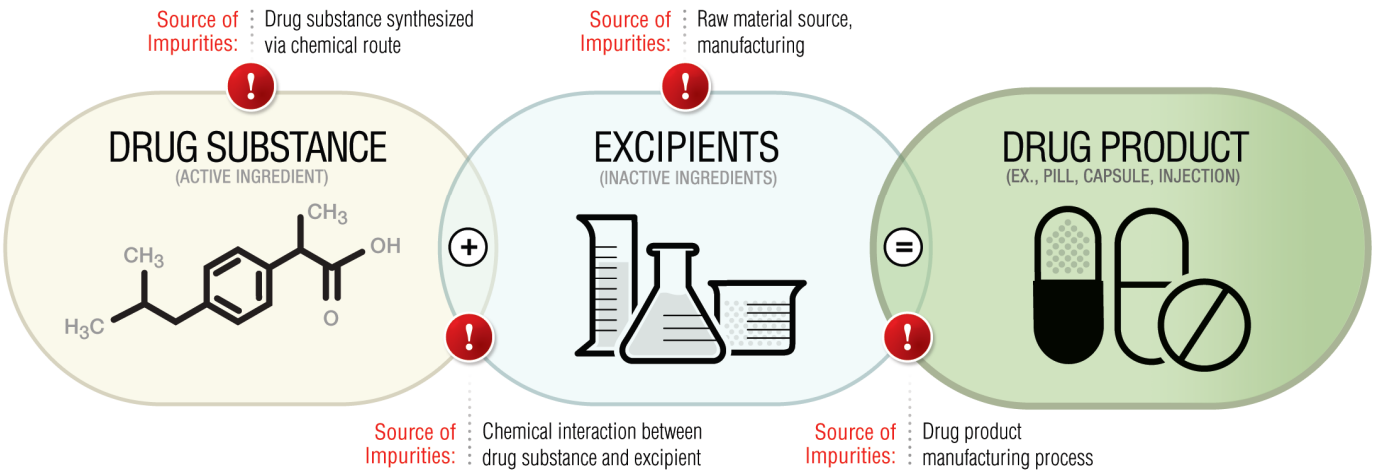
Source of Impurities



The distribution of drug impurities in this database is based on origin illustrates a wide range of agents that are commonly encountered in drug development program. A comparison of public to private impurities by class is provided.

Valerio, L. G., & Cross, K. P. (2012). Characterization and validation of an *in silico* toxicology model to predict the mutagenic potential of drug impurities. *Toxicology and Applied Pharmacology, 260*(3), 209-221.

Source of Impurities



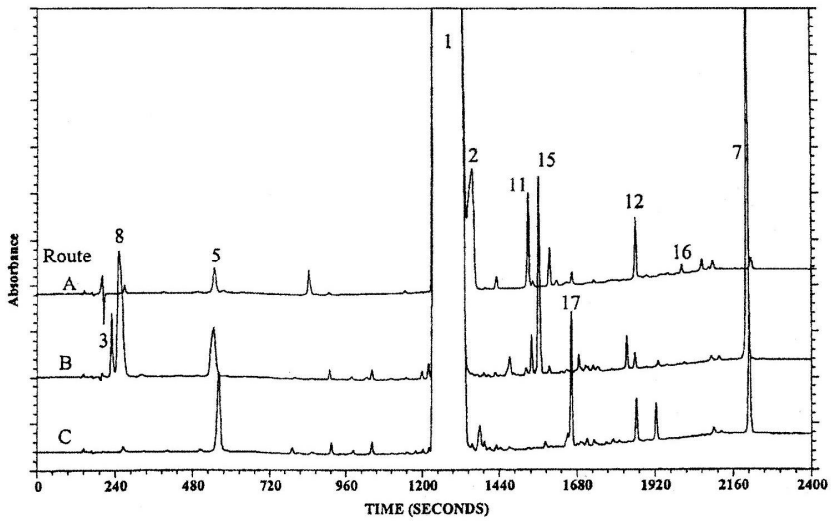
- **Question:**
  - If a manufacturer controls impurities and degradation products in accordance with only a pharmacopeial monograph, is that acceptable to the regulators
- **Answer**
  - Monographs based upon how the drug substance and drug products was prepared historically.
  - A particular manufacturer's manufacturing method for formulation components may lead to unexpected impurities, due to a different route of synthesis, different reagents, etc. Different processes may lead to different impurities.
  - If an individual monograph is inadequate to control an impurity, the manufacturer is responsible for developing and validating appropriate analytical procedures, establishing acceptance criteria, and communicating with USP.

Sources of Process Impurities

Organic impurities

- Last step intermediates
- Reagents (carried over as trace impurities)
- Side reactions(incomplete reaction, over-reaction, isomerization, rearrangement)
- Impurities in starting materials (positional isomers) or their reaction products
- Impurities from multiple synthetic routes
  - Identity and amounts of impurities vary as a function of the synthetic route
  - Synthetic route might change during the development of a product
  - Generic manufacturers might use different routes
  - e.g., Paroxetine Hydrochloride synthesized by many different procedures and analyzed by more than one LC procedure.

Chromatograms of Products by Three Synthetic Routes



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Investigation of Impurities – Impurity Profile

1. What are the potential impurities?
2. What impurities are likely to be present?
3. Impurity profiling – Requirements?
4. Control of impurities – How?

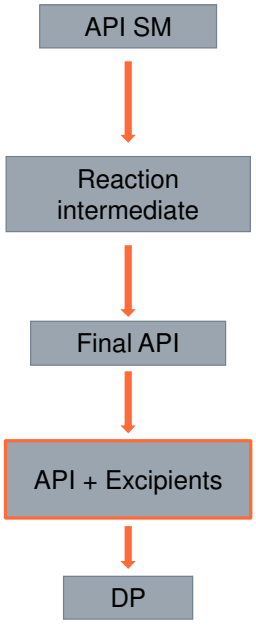
Investigation of Impurities

- Understand the origin of impurities
- Understand mechanisms for minimization or removal of impurities

Structural characterization of impurities and of degradation products is an integral part of the pharmaceutical product development

- Essential for
  - Production of a high-quality product shown to be safe
  - Optimization of the production process of the drug substance and of the drug product
  - Development of better formulations
  - Development of suitable storage conditions
  - Fulfilling requirements of regulatory agencies

What are the Potential Impurities?



Potential Impurities

API Starting Material (SM)
Intermediates

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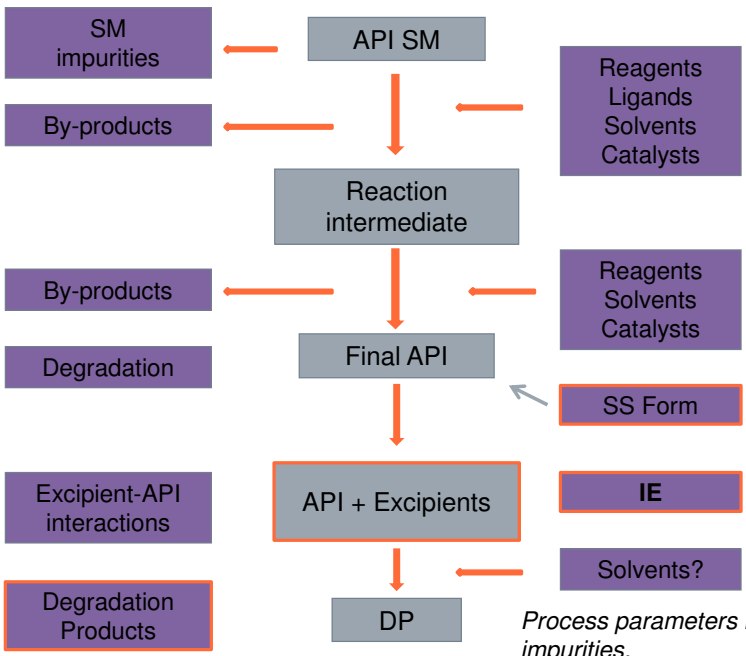
What are the Potential Impurities?



Potential Impurities

Starting material (SM)
Intermediate
Impurities - SM
Reagents
Ligands
Solvents
Catalysts
Reaction by-products
Degradation products
Excipient-API interactions
Impurities in Excipients (IE)
Impurities in Solvents
Impurities in Reagents
Solid state Forms

Process parameters like Temp., Time and pH are critical in the control of impurities.

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What are the Potential Impurities?

For Drug Substance

- It is essential to have a detailed knowledge of the preparation of the DS.
- Starting materials, reaction intermediates, reagents and solvents should be controlled at each stage of the synthesis.
- It is essential to know how the DS degrades.
  - Forced degradation studies of the drug substance

What are the Potential Impurities?

For Drug Product

- Knowledge of the Formulation process should be essential. Are there solvents involved, heat, water, etc.?
- Most of the potential impurities in formulation arise during the formulation process and its subsequent degradation.
- The focus of DP impurities is usually limited to degradation products.
- At times focus on API-Excipient and API-API interactions in combination Products.

What are the Potential Degradation Impurities?

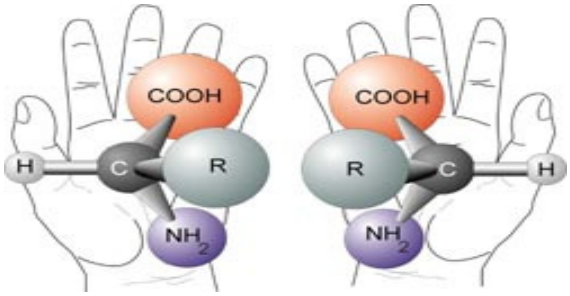
- These can be determined from the results of stress studies preferably of the drug product.

  Types of reaction causing degradation

  - Hydrolysis
  - Oxidation
  - Photolysis (e.g., cis/trans isomerization)
  - Elimination
- Significant degradation products should be identified and treated as potential impurities.

Chiral Impurities

- Many drugs have one or more chiral centers
- Several drugs have been developed as single enantiomer products so the undesired enantiomer is considered an impurity

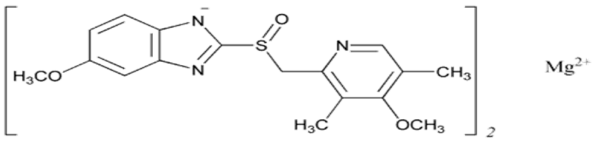


Safety Concerns for Chiral Drugs

- Enantiomers of chiral drugs are of concern because:
  - Only one enantiomer may be active
  - Enantiomers may have different activities
  - Undesirable enantiomer may be inactive but causes increased metabolic burden
  - Undesirable enantiomer may be toxic (e.g., thalidomide, dextromethorphan)
- FDA Policy Statement for the Development of New Stereoisomeric Drugs (1992)
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm

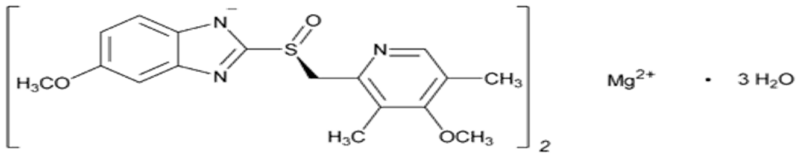
Chiral and Racemic Drugs

Some drugs have been developed as racemates and later introduced as single isomer products



Omeprazole Mg

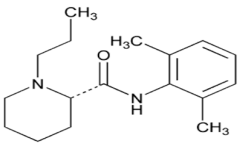
USP requirements
Specific rotation: between +0.5 and 0.5 deg



Esomeprazole Mg (S-isomer of omeprazole)

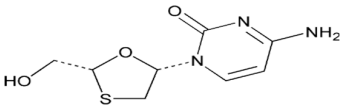
USP requirements
Specific rotation: between -137 and -142 deg
Enantiomeric purity: Not more than 0.2% of the R-enantiomer

Examples

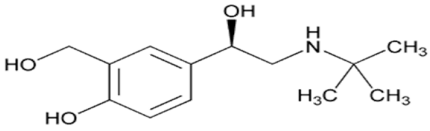


· HCl

Ropivacaine HCl, NMT 0.5% of the *R* isomer by CE
Ropivacaine HCl Injection, NMT 2.0% *R* isomer by HPLC, chiral HPLC ID by retention time

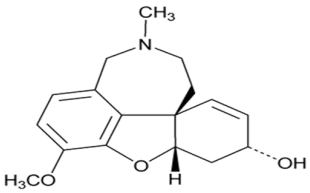


Lamivudine, NMT 0.3% of the *S* isomer by HPLC, chiral HPLC ID



· HCl

Levalbuterol HCl, NMT 0.2% of the *S* isomer by HPLC, chiral HPLC ID by retention time
Levalbuterol inhalation solution, NMT 2.5% by HPLC



· HBr

Galantamine HBr, NMT 0.10% of the 4R,8R stereoisomer

Other examples: Rivastigmine tartrate, Montelucast Na, Dexmedetomidine HCl, Benazepril HCl, Esomeprazole Mg

Impurity Control Summary

Input controls	Quality of starting materials, reagents, solvents, excipients
Process controls	Reaction conditions, purification points, critical process parameters and ranges, intermediate controls, production and storage conditions, process analytical technology
API and drug product quality	Verification of quality through final assays

- Process and degradation chemistry knowledge leads to necessary controls

Impurity Profiling - Pathways

- *Impurity profiling*
  - Separation, identification/structure elucidation (use of modeling software), quantitative determination
- Separation by techniques
  - HPLC, GC, CE and TLC
  - others (detection sensitivity essential)
- Identification/structural elucidation
  - Identification: Use of selective detectors in combination with separation techniques.
    - LC-UV –useful for identification but not for structural elucidation
    - LC-MS useful for both identification and structural elucidation
    - LC-IR useful but cumbersome
    - LC- NMR absolute technique for structural identification but expensive
  - Matching mobility with authentic samples of potential impurities (not less than two orthogonal systems)

Impurity Profiling - Pathways

- Isolation (Preparative chromatography)
  - Synthesis may be needed for structural confirmation
- Evaluation of their toxicological properties

  Part of qualification of impurity
- Development of method for quantitative determination

Impurity Profiles – When?

- Determined at the time of
  - Initial IND filing
  - NDA filing
  - Post NDA approval
  - ANDA Filing
- Monitored ongoing basis
- Reconfirmed after changes in
  - Synthesis of the bulk drug substance
  - Drug product process or formulation

Discussion

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Contents

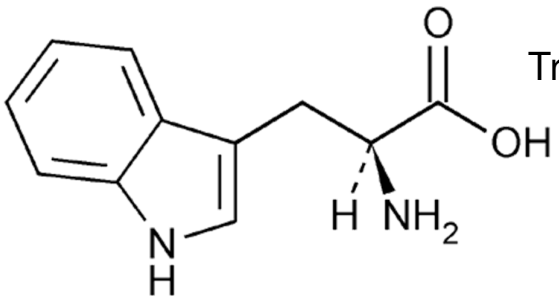
Setting Limits for Impurities

- Limits must be set for the process impurities and degradation products.
- **Such limits are fundamental to ensuring the identity, strength, quality, and (chemical) purity of the drug substance or drug product.**

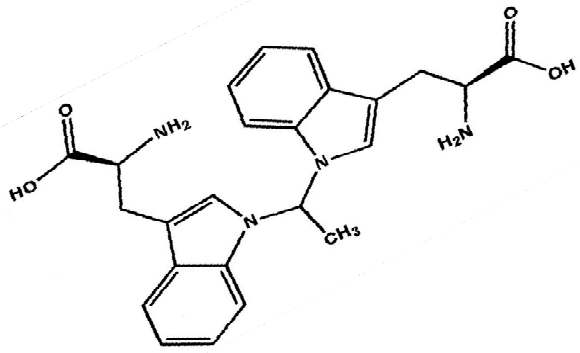
What are the Factors Influencing the Limits?

- Toxicology of impurities relative to a drug substance;
- Route of administration, e.g., oral, topical, or parenteral;
- Daily dose, i.e., frequency and amount administered of a drug substance;
- Target population (age and disease state), e.g., neonates, children, or senior citizens;
- Toxicology of an impurity, when appropriate;
- Source of a drug substance, e.g., synthetic, natural product, or biotechnology;
- Duration of therapy, i.e., administration over a long period (treatment of chronic conditions) versus administration intended for a short duration (treatment of acute conditions);
- Capability of a manufacturer to produce consistently high-quality final product.

2010 USP Tryptophan Monograph



Tryptophan



Tryptophan Related Compound A = EBT (Dimerization product)

Tryptophan Monograph USP 31

- **Assay** by titration with perchloric acid. Limits 98.5% - 101.5%
- **Specific rotation** -29.4° -32.8°
- **Purity** tests: pH, LOD, Residue on ignition, Chloride, Sulfate, Arsenic, Iron, Heavy metals
- No Organic impurities test

Tryptophan Monograph USP 32

Included Organic Impurities Tests

Organic impurities, Procedure 1:

Acceptance criteria

Total impurities 1: NMT 0.01% of the total impurities eluting prior to the tryptophan peak

Total impurities 2: NMT 0.03% of the total impurities eluting after the tryptophan peak. [Note—Exclude the peak for tryptophan related compound B.]

Tryptophan related compound A: If a peak for tryptophan related compound A is observed in the Sample solution, then perform the test for Procedure 2: Limit of Tryptophan Related Compound A, below.

Procedure 2: Limit of Tryptophan Related Compound A

Acceptance criteria: **NMT 10 ppm** Tryptophan Related Compound A

Setting Acceptance Criteria for Impurities

- If there is a monograph in the USP that includes a limit for a specified impurity, FDA recommends that the acceptance criterion be set no higher than the official compendial limit.
- If the level of a specified impurity is above the level specified in the USP, FDA recommends qualification. Then, if appropriate qualification has been achieved, an applicant can petition the USP for revision of the acceptance criterion.
- If a limit for a specified impurity does not exist in the USP, FDA recommends that you qualify the impurity by comparing it to the observed amounts of the impurity in the reference listed drug product (RLD). Your acceptance criterion should be similar to the level observed in the RLD. Alternatively, the acceptance criterion may be set based on a qualified level that is justified by scientific literature, metabolite data, or toxicity studies.

Setting Acceptance Criteria for Impurities (cont.)

An impurity is considered qualified for an ANDA when one or more of the following conditions are met:

- The observed level and proposed acceptance criterion for the impurity do not exceed the level justified by the reference listed drug product.
- The impurity is a significant metabolite of the drug substance.
- The observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
- The observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in toxicity studies.

USP General Chapters for Impurities: <476> & <1086>

Modernization of Organic Impurities Testing in USP Drug Substance and Drug Product Monographs

- *Stimuli Article published in PF* 40(3) [May-June 2014]
- Acknowledged Survey Results
- Recommend Updates to General Notices *5.60 Impurities and Foreign Substances* after the final text for both chapters is developed
- Provide an Implementation Strategy

<476> Organic Impurities in Drug Substances and Drug Products

- New general chapter

<1086> Impurities in Drug Substances and Drug Products

- Extensive revisions proposed to existing general chapter

USP General Chapters for Impurities: <476> & <1086>

<476> Organic Impurities in Drug Substances and Drug Products

- First published in *PF* 40(3) [May-June 2014]
- Republished in *PF* 41(3) [May-June 2015],
  PF 43(6) [Nov-Dec, 2017]
  PF 45(1) [Jan-Feb, 2019]

<1086> Impurities in Drug Substances and Drug Products

- First published in *PF* 40(3) [May-June 2014]
- Republished in *PF* 41(3) [May-June 2015],
  PF 43(6) [Nov-Dec, 2017]
  PF 45(1) [Jan-Feb, 2019]

Discussion

Empowering a healthy tomorrow

USP Education

Contents

ICH Guidelines

- ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories.
  - **Q** *"Quality" Topics*
  - **S** *"Safety" Topics*
  - **E** *"Efficacy" Topics*
  - **M** *"Multidisciplinary" Topics*

http://www.ich.org/products/guidelines.html

ICH "Q" (Quality) Guidelines

- Q1 Stability
- Q2 Analytical Validation
- Q3 Impurities
- Q4 Pharmacopoeias
- Q5 Quality of Biotechnological Products
- Q6 Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System

ICH Guidelines Specifically Addressing Impurities

- Q1A – "Stability Testing of New Drug Substances and Products"
- Q1B – "Photo-stability Testing of New Drug Substances and Products"
- Q2A – "Text on Validation of Analytical Procedures"
- Q3A – "Impurities in Drug Substances"
- Q3B – "Impurities in Drug Products"
- Q3C – "Impurities: Residual Solvents"
- Q3D – "Elemental Impurities" – in progress
- Q6A – "Specifications: test procedures and acceptance criteria for new drug substances and new drug substances; chemical substances"
- M7 – "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" – in progress

Definitions in Q3A(R2) and Q3B(R2)

- **Identification (Reporting) Threshold**: A limit above which an impurity (degradation product) should be identified (reported)
- **Qualification Threshold**: A limit above which an impurity (degradation product) should be qualified
- **Reporting Threshold**: A limit above which an impurity or degradation product should be reported.
- **Specified Impurity (Degradation Product)**: An impurity (degradation product) that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. Can be either identified or unidentified.

Definitions in Q3A(R2) and Q3B(R2)

Continued…

- **Unspecified Impurity (Degradation Product)**: An Unspecified Impurity is an impurity that is limited by a general acceptance criterion, but is not individually listed with its own specific acceptance criterion, in the *existing* drug substance specification.
- **Identified Impurity (Degradation Product)**: An impurity for which a structural characterization has been achieved.
- **Unidentified Impurity (Degradation Product)**: An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

ICH Reporting and Control of Impurities Expectation and Requirements (Q3A and Q3B)

- **Organic Impurities**
  - List of actual and potential impurities [total and individual impurities, identified and unidentified for all batches (in various stages of the development)]
  - Scientific appraisal of synthetic pathways
  - Degradation pathways and potential impurities generated during manufacture, storage, and stability studies
  - Impurities associated with raw materials
  - Studies conducted to detect and identify impurities (including stress testing)
  - Impurities arising from the interaction with excipients and/or the immediate container closure system

Thresholds for Impurities in New Drug Substances (% of Drug Substance)

Maximum Daily Dose (g)	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
> 2	0.03%	0.05 %	0.05 %

Exercise – Drug Substance

- Drug substance is to be is used in a formulation
- Maximum daily dose is 0.5g of the drug substance
- % of Impurity A observed 0.044%
- % of Impurity B observed 0.096%
- % of Impurity C observed 0.12%
- % of Impurity D observed 0.1649%
- Based on the ICH guidelines Q3A determine the required actions

Clue: calculate the daily intake amount of the impurity

Exercise – Sample Calculation

Imp A 0.044%

TDI of Imp A = (0.04/100) x 500mg/day = 0.2 mg/day or 0.04%/day

ID Threshold >0.10% or 1mg/day

0.04% of Imp A is lower than both 0.10% or 1 mg/day

Imp D 0.1649

TDI of Imp D =(0.16/100) x 500 mg/day = 0.8 mg/day or 0.16%

ID Threshold >0.10% = ID needed

Qual threshold >0.15% =Qualification needed

Thresholds for Impurities in New Drug Substances (% of Drug Substance)

Maximum Daily Dose (g)	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
> 2	0.03%	0.05 %	0.05 %

Illustration of Reporting, Identification, Qualification of Impurities

Example 1: 0.5 g Maximum Daily Dose

- Reporting threshold = 0.05%
- Identification threshold = 0.10% or 1mg/day(use the lower)
- Qualification threshold = 0.15% or 1mg/day(use the lower)

"Raw" Observed Result (%)	Result to be Reported (%)	Calculated Total Daily Intake (TDI) (mg) of the Impurity	Action Identification	Action Qualification
Imp A 0.044	Not reported	0.2 mg	none	none
Imp B 0.0963	?	?	?	?
Imp C 0.12	?	?	?	?
Imp D 0.1649	0.16	0.8	ID needed	Qualification needed

Illustration of Reporting, Identification, Qualification of Impurities

Example 1: 0.5 g Maximum Daily Dose

- Reporting threshold = 0.05%
- Identification threshold = 0.10% or 1mg/day (use the lower)
- Qualification threshold = 0.15% or 1mg/day (use the lower)

"Raw" Observed Result (%)	Result to be Reported (%)	Calculated Total Daily Intake (TDI) (mg) of the Impurity	Action Identification	Action Qualification
Imp A 0.044	Not reported	0.2	None	None
Imp B 0.0963	0.10	0.5	None	None
Imp C 0.124	0.12	0.6	ID Needed	None
Imp D 0.1649	0.16	0.8	ID Needed	Qualification Needed

Thresholds for Impurities and Degradation Products in New Drug Products

	Degradation Product Thresholds					
Maximum daily dose	< 1mg	1-10mg	> 10-100mg	> 100mg-1 g	> 1-2g	> 2g
Reporting	0.10%	0.10%	0.10%	0.10%	0.05%	0.05%
Identification[a]	1.0% or 5µgTDI[b]	0.5% or 20µgTDI[b]	0.2% or 2mgTDI[b]	0.2% or 2mgTDI[b]	0.2% or 2mgTDI[b]	0.10%
Qualification[a]	1.0% or 5µgTDI[b]	1.0% or 50µgTDI[b]	0.5% or 200µgTDI[b]	0.2% or 3mgTDI[b]	0.2% or 3mgTDI[b]	0.15%

[a] Lower threshold may be appropriate for toxic impurities
[b] Whichever is lower, calculated value or Total Daily Intake (TDI)

Exercise – Drug Product

- Tablet Y is to be is used in a formulation
- Maximum daily dose is 50 mg of the active drug in each tablet
- % of degradant A observed 0.04%
- % of degradant B observed 0.21%
- % of degradant C observed 0.12%
- % of degradant D observed 0.55%
- Based on the ICH guidelines Q3B determine the required actions

Clue: calculate the daily intake amount of the impurity

Thresholds for Impurities and Degradation Products in New Drug Products

	Degradation Product Thresholds					
Maximum daily dose	< 1mg	1-10mg	> 10-100mg	> 100mg-1 g	> 1-2g	> 2g
Reporting	0.10%	0.10%	0.10%	0.10%	0.05%	0.05%
Identification[a]	1.0% or 5µgTDI[b]	0.5% or 20µgTDI[b]	0.2% or 2mgTDI[b]	0.2% or 2mgTDI[b]	0.2% or 2mgTDI[b]	0.10%
Qualification[a]	1.0% or 5µgTDI[b]	1.0% or 50µgTDI[b]	0.5% or 200µgTDI[b]	0.2% or 3mgTDI[b]	0.2% or 3mgTDI[b]	0.15%

[a] Lower threshold may be appropriate for toxic impurities
[b] Whichever is lower, calculated value or Total Daily Intake (TDI)

Illustration of Reporting, Identification, Qualification of Degradation Products

Example 1: 50 mg Maximum Daily Dose

- Reporting threshold: 0.1%
- Identification threshold: 0.2% or 2 mg (use the lower)
- Qualification threshold: 0.5% or 200 µg (use the lower)

"Raw" Observed Result (%)	Result to be Reported (%)	Calculated Total Daily Intake (TDI) (µg) of the Impurity	Action Identification	Action Qualification
Deg A 0.04	?	?	?	?
Deg B 0.2143	?	?	?	?
Deg C 0.349	?	?	?	?
Deg D 0.550	?	?	?	?

Illustration of Reporting, Identification, Qualification of Degradation Products

Example 1: 50 mg Maximum Daily Dose

- Reporting threshold: 0.1%
- Identification threshold: 0.2% or 2 mg/day (use the lower)
- Qualification threshold: 0.5% 200 µg (TDI)

"Raw" Observed Result (%)	Result to be Reported (%)	Calculated Total Daily Intake (TDI) (µg) of the Impurity	Action Identification	Action Qualification
Deg A 0.04	Not reported	20	None	None
Deg B 0.2143	0.2	100	None	None
Deg C 0.349	0.3	150	ID Needed	None
Deg D 0.550	0.6	300	ID Needed	Qualification Needed

Impurity Qualification

- For impurities known or likely to exceed qualification threshold consider conducting -
- General toxicity studies: one or more studies should be designed to allow comparison of unqualified to qualified material
  - Performed in the species most likely to maximize the potential to detect the toxicity of a degradation product or process impurity
  - 14 to 90 days
- Genotoxicity studies
  - Point mutations (e.g., Ames)
  - In vitro chromosomal aberrations
- Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate
- Consider patient population and duration of use in study design

ICH M7 – Genotoxic Impurities

- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- Step 4 of ICH process

https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf

Guideline includes excellent appendices

- Appendix 1: Scope Scenarios for Application of the ICH M7 Guideline
- Appendix 2: Case Examples to Illustrate Potential Control Approaches
- Appendix 3: Addendum to ICH M7 (includes 14 common genotoxic impurities)

ICH M7 – Genotoxic Impurities

- Impurities must be assessed for genotoxic potential
- For potentially genotoxic impurities (GTIs), acceptance limits lower than ICH Q3 may be necessary.

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

Table 3: Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

ICH M7 – Other Considerations

- Not applied to products for advanced cancer indications (see ICH S9)
- Not applied to drug substances that are themselves genotoxic
- Will be applied to changes in existing authorizations if new or greater levels of previous impurities are present
- Assess potentially genotoxic impurities which may be present at levels below the Q3 A/B ID thresholds (same as current guidelines)
- Previous data from similar compounds may be used with justification to discharge risk
- Description of acceptable control mechanisms (specifications, purge studies, control at intermediates)

FDA Guidance for Industry
NDAs: Impurities in Drug Substances and Drug Products

- For NDA:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070577.pdf
- For ANDA:
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072861.pdf.

MaPP (FDA): Effective on September 19, 2018

MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5017.2

POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Table of Contents

MaPP (FDA): POLICY

POLICY

1. The terminology described in ICH Q3A(R2), Q3B(R2), and Q6A should generally be applied to NDA and ANDA products. Specifically, a specification should include the following, where "specified impurity" is any impurity present at greater than the identification threshold:

Drug Substance

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Drug Product

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold
- Total degradation products

MaPP (FDA):

- For more details on the new guidelines:
  https://www.fda.gov/media/124859/download
- Effective on Sep 19, 2018.

FDA Guidance for Industry
Impurities in New Veterinary Drug Substances

- Same classification and sources as in human drugs
- Similar approaches and reporting requirements (specifications and analytical procedures)
- Specifications to include list of impurities (organic, inorganic, residual solvents)

Discussion

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USP Education

Contents

Impurities in Pharmacopeias

- General Notices
- General Chapters
- Requirements in Individual Monographs
- Reference Standards are provided where required
- The United States Pharmacopeia
- European Pharmacopeia
- British Pharmacopeia and Japanese Pharmacopeia

Structural Hierarchy in USP

- General Notices (GN)
  - Overarching – Apply to all chapters and monographs
- General Test Chapters
  - Under <1000 tests and assays applying to multiple monographs
  - General Information Chapters above <1000>
  - Do not contain specifications

Monographs: API, Excipients, Drug Products

- Supersede both GN and Chapters

General Notices

- *"The specification in a monograph consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and **purity** of the article."*
- Concepts about purity change with time and developments in analytical chemistry
- Information about impurities – essential for the quality and safety of a drug product

General Notices

5.60.10. Other Impurities in USP and NF Articles

- *"If a USP or NF monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading Other Impurity(ies)."*
- A material produced by a different synthetic route than that used for the development and validation of the official monograph may contain different impurities

Other Impurities Under General Notices

- *"The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all Other Impurities combined with the monograph-detected impurities may not exceed 2.0% unless otherwise stated in the monograph."*
- A manufacturer must identify "other" impurities if they are >0.1% and declare them on the Certificate of Analysis (consistent with ICH Q3A)

USP General Chapters for Impurities

- *USP official General Chapters for impurities in Drug Substances and Drug products:*
  - *USP* <466> *Ordinary Impurities*
  - *USP* <1086> *Impurities in Drug Substances and Drug Products*

USP <466> Ordinary Impurities

- Ordinary impurities are defined as those species in drug substances and/or drug products that have no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles
- Default limit: NMT 2.0%
  - Methodology (older) —
    - Estimation by relative methods rather than by comparison to individual Reference Standards
    - Typical evaluation methods by thin-layer chromatographic (TLC) techniques
- About 70 *USP* monographs refer to *USP* <466>
- Plan is to obsolete *USP* <466> and replace with HPLC testing of impurities using specific organic impurities testing and RS

USP <1086> Impurities in Drug Substances and Drug Products

- Informational Chapter
- Introduced in early 2000; revised in 2010
- Needs to be revised to reflect the current thinking of ICH & FDA
- Created an Expert Panel to handle this project
- Panel recognized the need to have a separate chapter that can have enforceable information

USP <1086> Continued

Modernization of Organic Impurities Testing in USP Drug Substance and Drug Product Monographs

- *Stimuli Article published in PF* 40(3) [May-June 2014]
- Acknowledged Survey Results
- Recommendations:
  - Updates to General Notices *5.60 Impurities and Foreign Substances* and *5.60.10. Other Impurities in USP and NF Articles* after the final text for both chapters is developed
  - Develop a new enforceable general chapter for impurities
- Provide an Implementation Strategy (delay implementation)

USP <1086> Revision *PF* 40(3) – May - June 2014

Scope includes:

- To align with current scientific and regulatory standards
- Introduce definitions aligned with ICH Q3A and Q3B
- Provide guidelines for control of all impurities in drug substance and drug products (elemental impurities, residual solvents, and organic impurities)
- Introduce a decision tree to address organic impurities in drug substances and drug products
- Provide additional sources of information and guidance

USP <1086> Revision *continued*

- Published to address public comments in *PF* 41(3) [May-June -2015]
- More comments were received
- Republished the revision in *PF* 43(6)-Nov-Dec
- Republished the revision in *PF* 45(1)-Jan-Feb 2019 – extended comments deadline May 31, 2019

USP <476> Organic Impurities in Drug Substances and Drug Products

New Chapter published in *PF* 40(3) May - Jun, 2014

Scope includes:

- Enforceable chapter
- Complementary chapter to <1086>
- Align with current scientific & regulatory approaches
- Threshold tables for drug substances and drug products
- Support appropriate control of impurities, particularly unspecified impurities/degradation products and total impurities/degradation products
- Available tool to be cross referenced in individual monographs, in a case-by-case basis (e.g., OTC articles)

USP <476> *continued*

- Published to address public comments in *PF* 41(3) [May-June -2015]
- More comments were received
- Republished the revision in *PF* 43(6)-Nov-Dec 2017
- Republished the revision in *PF* 45(1)-Jan-Feb 2019 – extended comments deadline May 31, 2019

Other General Chapters Related to Impurities

- *USP* <467>*Residual Solvents*
- *USP* <232>*Elemental Impurities*
- Chapters for other inorganic impurities (e.g.,: Selenium <291> Thiobendazole NMT 0.003%)
- *Residue on Ignition* <281> determines unidentified inorganic impurities
- *Loss on Drying* <731> determines unidentified volatiles
- *Metal Particles in Ophthalmic Ointments* <751> determines the number and size of discrete metal particles
- *Melting Range or Temperature* <741> purity and identity
- *Refractive Index* <831>
- *Particulate Matter in Injections* <788>

Other General Chapters Related to Impurities

Continued…

- **Completeness and Clarity of Solution <641> — Dacarbazine for Injection** When dissolved as directed in the labeling, it yields a clear, pale yellow to yellow solution
- ***Nitrogen Determination* <461> -** e.g., Dextrin – NMT 1.0% protein
- **Oxidizable substances** (persistence of the pink color of a permanganate solution) Monographs: Acetone, Lanolin et al

Impurities in USP Monographs

- Based on the sponsor's NDA/ANDA
- Limits of Specified impurities are consistent with FDA approved limits
- Limits of unspecified and total impurities are consistent with FDA approved limits
- Procedures are typically based on the approved NDA/ANDA methods; may not be identical

Impurities in USP Monographs

- Drug substances contain process impurities and may contain some degradants
- Drug products contain mainly degradation products
  - May include process impurities if they are also degradation products
- Distinction between process impurities and degradation products become more important when dealing with drug products

Discussion

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USP Education

Contents

- Introduction
  - History
  - Recalls
  - Definitions
  - Classification/Origin of Impurities
  - Investigation of impurities
  - Setting limits for impurities
- Guidelines/Guidances
  - ICH/FDA
  - Pharmacopeias
- Non drug related impurities
  - Extractables and Leachables
  - Impurities due to Adulteration
  - Impurities in Water and Excipients

Impurities in Monographs

Case studies (Examples)

Flexible monographs

Possible Scenarios Regarding Impurities

- Manufacturer's impurity limits are different from *USP* Monograph or *Pharmacopeial Forum* (*PF)* proposal limits
  - Monograph or *PF* proposal Limits are wider than FDA approved limits
  - Monograph or *PF* limits are tighter than FDA approved limits
- Specific impurities of interest are not included in *PF* proposal or *USP* monograph
  - Multiple scenarios
- Resolution of each case with examples

Monograph Limits Different from FDA Approved Limits

- Two possible scenarios:
  - Monograph or *PF* proposal Limits are wider than FDA approved limits
    - This does not pose any compliance issue - no resolution necessary
  - Monograph or *PF* proposal limits are tighter than FDA approved limits
    - This does pose a compliance issue
    - Following example demonstrates the resolution

PF Proposal Limits are Tighter than Approved Limits

- New monograph proposal for ***Levetiracetam Tablets*** published in *Pharmacopeial Forum* 36(1) for Public comments

Name	Limit NMT %
Levetiracetam acid	0.1
Any unspecified degradation product	0.1
Total	0.35

Levetiracetam Tablets

- USP received the following comment from an approved application holder
  - Levetiracetam acid limit in *PF* proposal is tighter than FDA approved limit
- USP received the following comments from FDA
  - Levetiracetam acid limit is different from the approved limit
  - Total impurities limit in the *PF* proposal is different from the approved limit
  - Any individual unspecified degradation product should be tightened to 0.10% to be consistent with ICH Q3B guidelines

Levetiracetam Tablets

- Resolution steps:
- Contacted all the approved applicants
  - Highest approved limit for Levitiracetam acid NMT 0.3%
  - Highest limit for Total impurities NMT 0.6%
  - Confirmed the above with FDA
- Expert Committee decided to widen the limits of levetiracetam acid and Total Impurities to be consistent with FDA approved limits
- Expert Committee did NOT tighten the limit for “Any individual unspecified degradation product” from 0.1% to 0.10% because many approved applications have 0.1% limit

Levetiracetam Tablets

Official in *USP* <34> *Supplement* 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levetiracetam related compound B[a,b]	0.54	—	—
Levetiracetam	1.0	—	—
Levetiracetam related compound A[a,c]	1.7	—	—
Levetiracetam acid[d]	2.1	0.79	0.3
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.6

[a] These impurities are listed for information only; they are process impurities, which are controlled in the drug substance.
[b] (S)-2-Aminobutanamide.
[c] (S)-N-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.
[d] (S)-2-(2-Oxopyrrolidine-1-yl)butanoic acid.

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Specific Impurities Not Included

- Possible scenarios
  - Specific impurities come from a different synthetic route
  - Monograph sponsor may not have considered the specific impurities

Specific Impurities Not Included

- Information USP needs to know:
  - Regulatory status of the article as this is very important to decide the path
  - Has the company evaluated the USP monograph or *PF* procedure?
  - Provide supporting data for revision request

Trimipramine Maleate

Published in *PF* 32(6) for public comments

Name	RRT	Acc Criteria NMT%
Iminodibenzyl	0.49	0.20
Imipramine	0.72	0.20
Trimipramine Related compound A	0.80	0.20
Trimipramine	1.0	NA
Any unspecified impurity	--	0.10
Total	---	0.50

Trimipramine Maleate

- USP received the following comments from an approved application holder
  - *PF* proposal does not include three additional impurities.
  - Request USP to include their in-house procedure
- USP observations:
  - Commenter's in-house procedure does not monitor Trimipramine Related Compound A

Trimipramine Maleate

- Resolution Steps
  - Commenter was asked to evaluate the *PF* 32(6) procedure
  - Results of the evaluation indicated *PF* 32(6) procedure to be suitable to monitor all the impurities
  - Commenter provided the evaluation study report
  - Expert committee decided to include the new impurities with FDA approved limits

Trimipramine Maleate

Became Official in *USP* <34> *Supplement* 2

Name	RRT	Acc Criteria NMT%
Trimipramine N-oxide	0.32	0.15
Iminodibenzyl	0.49	0.20
Desmethyltrimipramine	0.68	0.15
Imipramine	0.72	0.20
Trimipramine Related compound A	0.80	0.20
Trimipramine	1.0	NA
Trimipramine diamine	2.4	0.30
Any unspecified impurity	--	0.10
Total	---	1.0

Discussion

Empowering a healthy tomorrow

USP Education

Nicotine Transdermal System

Published in *PF* 42(2) for public comments

- USP received the following comments from an approved application holder
  - *PF* proposal impurity profile and limits are not consistent with their approved application
  - Request USP to include their in-house procedure with their approved limits
- USP observations:
- No supporting data from the commenter

Nicotine Transdermal System

Revision proposal first published in *PF 42(2)March-April 201*

- Scope: Monograph update - Introduce a procedure for *Organic Impurities* which can also be used for *Assay*.
- Manufacturer:
  - Based on a feasibility study per the new proposed Assay/Impurities test, the proposed extraction solvent (Methanol: tetrahydrofuran = 90:10) failed to extract nicotine completely. *Assay* is deemed not suitable for their product.
  - The proposed impurity profile and limit as listed in the Table 8 of the proposed monograph do not align with the impurity profile and limits of our marketed product approved by FDA
- FDA: Organic Impurities specifications are inconsistent with what has been approved

Nicotine Transdermal System

	USP proposed monograph	Commenter's Method
# sample per prep	composite of 10	10 individual preps
Sample Stock, mg/mL	1 mg/mL	0.72, 1.56, 2.28 mg/mL for size 7, 14, 21
Sample dilution, mg/mL	0.05 mg/mL in MP A	0.046, 0.047, 0.043 mg/mL in water
Delamination Solvent	9:1 MeOH: THF	4 hrs in 10 mL MeCl2 , then 1 hr stirring with 50 mL of 0.425% phosphoric acid
MP A	pH 7.5-7.6, phosphate buffer	pH 4.95 0.055% Dodecanesulfonate
MP B	MeOH	Acetonitrile
Profile	gradient	isocratic (78:22 A:B)
Detector wavelength	260 nm	254 nm
HPLC Column	C18	C18
Column Temp ℃	45 ± 2	Ambient
Standard	0.05 mg/mL nicotine in MP A	0.005 - 0.068 mg/mL nicotine in water

Nicotine Transdermal System continued

Possible scenarios

- Procedures contain two components:
  - Sample preparation
  - HPLC procedure
  - Need to understand what contributes to the low recovery

Nicotine Transdermal System

- USP request to the commenter:
  - Prepare the samples both by *PF* proposal procedure and the in-house procedure
  - Analyze both samples by both *PF* proposal procedure and in-house procedure
  - Submit the results with conclusions of the comparative analysis
  - Approved specifications along with chemical structures of the impurities

Nicotine Transdermal System

Conclusions of the commenter evaluation - Assay

- Parallel test results showed a good agreement between the USP and the in-house methods. All lot clearance batches and the stability samples passed the proposed
- This study demonstrates that the results from in-house method and the proposed USP test method (with in-house sample preparation) are similar.
- Assay procedure is suitable as long as the sample preparation differences can be accommodated

Nicotine Transdermal System

Conclusions of the commenter evaluation - Organic impurities

- Approved specifications for all size systems are in general higher for RC-C, RC-D for each dose strength
- Total degradation products limits are wider than the PF proposal limits
- Request the specifications for specified impurities, unspecified impurities, and total degradation products be widened to be consistent with FDA approved limits for the various dose strengths

Nicotine Transdermal System

- USP Contacted FDA with the updated specifications and the commenter's approved specifications.
- FDA initially did not agree because the approval was for the limit of each degradation product was on the basis of amount/transdermal system.
  - This is not correct as this would prevent comparing other approved proved products. Normalization is to%w/w is necessary
- FDA concurred with the widening of the specifications based on %w/w after internal discussions.
- Monograph official in USP43 Supplement 2

Final Monograph USP41 Supplement 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)		
Dose strength			7mg (*PF*)	14 mg (*PF*)	21 mg (*PF*)
Nicotinic acid[1]	0.15	1.3	0.5 (0.5)	0.5(0.5)	0.5(0.5)
Nicotine related compound E (1R,2S isomer)	0.25	0.76	0.5 (0.5)	0.5(0.5)	0.5(0.5)
Nicotine related compound E (1S,2S isomer)	0.27	0.76	0.5 (0.5)	0.5(0.5)	0.5(0.5)
Nicotine related compound F[2]	0.38	—	—	—	—
Nicotine related compound C[3]	0.54	1.0	2.8 (0.5)	2.6 (0.5)	1.8(0.5)
Nicotine related compound G[2]	0.64	—	—	—	—
Nicotine related compund A[4]	0.74	—	—	—	—
Nicotine related compound D	0.85	1.6	5.6(0.5)	3.2(0.5)	2.6(0.5)
Nicotine	1.00	—	—		
Nicotine related compound B[5]	1.19	1.9	0.5 (0.5)	0.5(0.5)	0.5(0.5)
Any other unspecified degradation product	—	1.0	0.6 (0.5)	0.5(0.5)	0.5(0.5)
Total degradation products	—	—	8.3 (2.0)	5.8(2.0)	4.4(2.0)

Resolution Process in Case of Discrepancy

1. Evaluate the issue
   a. If the discrepancy is in the monograph/ proposal limits, contact the Scientific Liaison
   b. If the discrepancy is regarding the procedure, do the following:
      - Evaluate what is not working.
2. Confirm correct column and parameters have been used
   a. Column information is available in *Pharmacopeial Forum* Briefing
   b. Information is also available form the on-line *USP–NF*
   c. USP chromatography column data base freely available on line http://www.uspchromcolumns.com
   d. Make adjustments per *USP* <621>
   e. If the adjustments resolve the issue, perform verification as needed
   f. If the issues persist, contact the Scientific Liaison with the Evaluation Study data

Discussion

Empowering a healthy tomorrow

USP Education

Contents

- Introduction
  - History
  - Recalls
  - Definitions
  - Classification/Origin of Impurities
  - Investigation of impurities
  - Setting limits for impurities
- Guidelines/Guidances
  - ICH/FDA
  - Pharmacopeias
- Non drug related impurities
  - Extractables and Leachables
  - Impurities due to Adulteration
  - Impurities in Water and Excipients

Impurities in Monographs

Case studies (Examples)

Flexible monographs

Flexible Monograph Examples

- ***Need-based*** flexibility to account for different routes of synthesis, hydrates, solvates, polymorphs, or formulations
- Enables multiple procedures, preparations, and/or acceptance criteria within a single monograph
- Uses of the flexible approach
  - Multiple formulation-specific dissolution procedures
  - Multiple organic impurity procedures based on different impurity profiles
  - Hydrate-specific water limits/ranges
  - Polymorph-specific crystallinity requirement
- May need procedure-specific USP Reference Standards

Flexible Monographs: General Notices 4.10.10

▲ 4.10.10. Applicability of Test Procedures. A single monograph may include more than one test, procedure, and/or acceptance criterion for the same attribute. Unless otherwise specified in the monograph, all tests are requirements. In some cases, monograph instructions allow the selection of tests that reflect attributes of different manufacturers' articles, such as different polymorphic forms, impurities, hydrates, and dissolution. Monograph instructions indicate the tests, procedures, and/or acceptance criteria to be used and the required labeling.

The order in which the tests are listed in the monograph is based on the order in which they are approved by the relevant Expert Committee for inclusion in the monograph. Test 1 is not necessarily the test for the innovator or for the reference product. Depending on monograph instructions, a labeling statement is not typically required if Test 1 is used.

Flexible Monograph: Dissolution Tests

To address product specific Dissolution tests

- **Medium**
  - Composition
  - Volume
- **Apparatus**
  - Type
  - Rotation speed, dips, flow rate
- **Tolerances**
- **Any differences in the dissolution conditions and/or in the tolerances constitutes a new test**
- **Typically follow revision bulletin process**

Flexible Monograph: Dissolution Tests

- **Example monographs with multiple dissolution tests**
  - Diltiazem HCl Extended Release Capsules – 16 tests
  - Metformin Extended Release Tablets – 13 tests
  - Theophylline Extended Release Capsules – 10 tests
  - Tamsulosin HCl Capsules – 10 tests
  - Nifedipine ER Tablets – 10 tests
  - Bupropione Hydrochloride Extended Release Tablets – 22 tests

Flexible Monograph: Dissolution Tests

- Address product-specific dissolution tests
- Metformin Hydrochloride Extended-Release Tablets
  - Dissolution <711>
    - Test 1
    - Test 2: If the product complies with this test, the labeling indicates that it meets *USP Dissolution Test 2*.
    - Test 3: If the product complies with this test, the labeling indicates that it meets *USP Dissolution Test 3*.
    - Test 4: If the product complies with this test, the labeling indicates that it meets *USP Dissolution Test 4*.
    - Test 13: If the product complies with this test, the labeling indicates that it meets *USP Dissolution Test 13*.
  - Labeling: When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Flexible Monographs: Examples

- Paroxetine Hydrochloride (official)
- Ropinirole Hydrochloride (official)
- Methylphenidate Hydrochloride (official)
- Irinotecan Hydrochloride (official)
- Nicotine Polacrilex *PF* 44(1)
- Azithromycin *PF* 43(3)

Flexible Monograph:

To address different organic impurity profiles

- Ropinirole – include impurities table from 3 procedures
- Two submissions came from two companies simultaneously
- *PF* 36(1) published with two different procedures due to two different impurity profiles
- Comment received from a DMF holder about coelution of the oxime. Different impurity profile due to differences in synthetic route of the drug substance
- Proposal was published again in *PF* 38(6) with 3 impurity procedures

Final Monograph Ropinirole Hydrochloride

Name	Procedure 1	Procedure 2	Procedure 3
Open ring nitroderivative	0.15	Not applicable	Not applicable
Monopropyl ropinirole	0.15	0.2	Not applicable
N-Hydroxyropinirole	0.15	Not applicable	Not applicable
Ropinirole Related Compound B	0.15	0.3	0.15
Methylene ropinirole	Not applicable	0.2	Not applicable
Ropinirole isohexyl analog	Not applicable	0.3	Not applicable
Propylidine ropinirole	Not applicable	0.2	Not applicable
Ropinirole oxime	Not applicable	Not applicable	0.15
Ropinirole indole derivative	Not applicable	Not applicable	0.10
Any individual unspecified imp	0.10	0.10	0.10
Total	1.0	1.5	0.50

Flexible Monograph: Azithromycin

To address different impurity profiles

- Organic Impurities, Procedure 1
  - Use Organic Impurities, Procedure 1 when the impurity profile includes erythromycin A oxime and erythromycin A iminoether.
- **ORGANIC IMPURITIES, PROCEDURE 2**
  - Use *Organic Impurities, Procedure 1* when the impurity profile includes erythromycin A oxime and erythromycin A iminoether.
- USP received comments to delete the test for Organic Impurities, Procedure 1, because Organic Impurities, Procedure 2 is adequate enough to resolve all the impurities including erythromycin A iminoether and erythromycin A oxime .
  - Proposal appeared in *PF* 43(3)
  - Official in May 2019 with one organic impurity procedure

Flexible Monograph: Azithromycin

To address different polymorphic forms

- Water Determination, Method I <921>
  - Where it is labeled as anhydrous: NMT 2.0%
  - Where it is labeled as the dihydrate: 4.0%–5.0%
  - Where it is labeled as the monohydrate: 1.8%–4.0%, except that it may be 4.0%–6.5% when the requirements of the *Loss on Drying* test are met
- Labeling:
  - Label it to indicate whether it is anhydrous, or the monohydrate, or the dihydrate. The amorphous form is so labeled. Where the quantity of azithromycin is indicated in the labeling of any preparation containing Azithromycin, this shall be understood to be in terms of anhydrous Azithromycin ($C_{38}H_{72}N_2O_{12}$).

Flexible Monograph – Inorganic Impurities

Manufacturing process leads to specific inorganic impurities

Galantamine Hydrobromide (Pd)

- *PF* 33(3) proposal included a test for Limit for Pd.

An approved manufacturer commented as follows:

- Our process does not use Pd in the process.
- Resolution:
  - EC made the test optional with the following note

    Limit of Palladium – [Note-Perform the test if Pd is known process impurity]

Flexible Monograph – Residual Solvents

Manufacturing process leads to specific residual solvents with limits higher than *USP* <467>

- Rocuronium Bromide
- includes a test for Limit of 2-propanol with a limit of NMT 1.0%
- includes test for Limit of Acetic acid with a limit of NMT 5.0%
- Both have the note - **Perform this test only if analyte is a known organic manufacturing process impurity**.

Resolution Process in Case of Discrepancy

1. Evaluate the issue
   a. If the discrepancy is in the monograph/ proposal limits, or procedure, contact the Scientific Liaison
   b. If the discrepancy is regarding the impurity profile, contact the Scientific Liaison to seek suitable resolution.

      Provide data on what evaluation work has been done and conclusions

      If necessary, the Scientific Liaison will work with the Expert Committee to determine the need for flexible monograph approach

Discussion

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USP Education

Harmonization with other Pharmacopeias

- Raltegravir Potassium family – Harmonization with EP
  - Raltegravir Potassium
  - Raltegravir Tablets
  - Raltegravir Chewable Tablets
- Lacosamide family –Harmonization with EP
- Rotigotine –Harmonization with EP
- Rotigotine Transdermal System – Harmonization with BP

Harmonization with other Pharmacopeias

Raltegravir Potassium

- Compare Limit differences

Name	EP	USP
Raltegravir Amine (EP impurity A)	Not listed	0.15%
Raltegravir Formididyl analog (EP Impurity B)	Not listed	0.15%
Raltegravir oxalylacetohydrazide analog (EP Impurity C)	0.3% (with RRF)	0.20% (with no RRF)
Raltegravir Related Compound E (EP Impurity E)	0.15%	0.15%
EP Impurity F (Hydrolysis 1)	0.15%	0.20
EP Impurity G (Hydrolysis 2)	0.15%	0.15%
Any individual, unspecified impurities	0.10%	0.10%
Total	0.5%	0.7%

Harmonization with other Pharmacopeias

Raltegravir Tablets and Chewable Tablets

- USP:
  - The Assay and Organic impurities procedures in the Tablets monograph are different from that in the Chewable Tablets monograph
- EP:
  - The Assay and Organic impurities procedures in the Tablets monograph are same as that in the Chewable Tablets monograph

Harmonization with other Pharmacopeias

Rotigotine

Name	EP	PF	USP
Desthienyl rotigotine	0.15%	0.15%	0.30%
Rptigotine reated compound C	0.2%	0.2%	0.30%
Ethylrotigotine (EP Imp D)	Controlled as unspecified	0.10%	0.15%
Rotigotine N-oxide (EP Imp E)	Controlled as unspecified	0.10	Not listed
Acetyl rotigotine (EP Imp F)			0.15%
Rotigotine Realel compound G	0.2%	0.2%	0.30%
Rotigotine Retaed compound H	Controlled as unspecified	0.10%	No specification
Rotigotine O-tosylate (EP Imp I)	Controlled as unspecified	0.10%	0.15%
Rotigotine-O-thieneylethyl (EP Imp J)	Controlled as unspecified	0.10%	0.15
Any individual, unspecified impurities		0.10%	0.10%
Total		0.6%	1.0%

USP Education

Discussion

Empowering a healthy tomorrow

USP Education

Contents

- Introduction
  - History
  - Recalls
  - Definitions
  - Classification/Origin of Impurities
  - Investigation of impurities
  - Setting limits for impurities
- Guidelines/Guidances
  - ICH/FDA
  - Pharmacopeias
- Non drug related impurities
  - Extractables and Leachables
  - Impurities due to Adulteration
  - Impurities in Water and Excipients

Contents

- Introduction
  - History
  - Recalls
  - Definitions
  - Classification/Origin of Impurities
  - Investigation of impurities
  - Setting limits for impurities
- Guidelines/Guidances
  - ICH/FDA
  - Pharmacopeias
- Non drug related impurities
  - Extractables and Leachables
  - Impurities due to Adulteration
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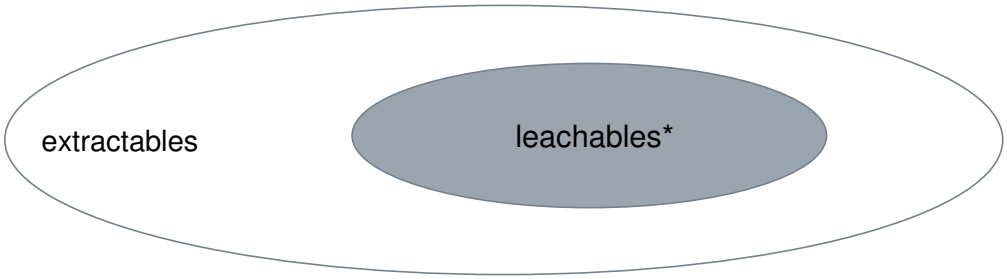
Extractables and Leachables

Extractable

- Any chemical species that can be removed from a packaging component under laboratory conditions (e.g., component pieces extracted with solvent).
- ***Leachable***
- Chemical compound that migrates from the primary packaging system into a drug product under storage conditions.

Migration from glass (metal oxides), rubber stoppers, plastic containers into DP



*not all leachables may be extractables

Regulatory Background

- Impurity guidelines
  - EMA Guideline
    - Guideline on the limits of genotoxic impurities (TTC)
  - ICH Guideline
    - Impurities in new drug substances (Q3A)
    - Impurities in new drug products (Q3B)
- What is being said:
  - Guidance on impurities focus on process related/degradation impurities **and leachables falls outside scope**
  - Guidance on genotoxic impurities **do not specifically cover the topic of leachables**
- Leachables are not drug related impurities and may potentially possess different toxic characteristics.
  - As such, analytical and qualification limits of leachable materials associated with a drug product, such as a pulmonary product, have been held to a higher standard than the approaches proposed in the ICH impurity guidelines

USP Guidance on Extractable and Leachable

USP <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*

- Chapter describes a framework for considering the issues associated with the proper design and justification of the extraction process used to assess the potential impact of contact between a packaging material and a drug product

USP <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*

- Chapter describes the development of scientifically supported testing and safety evaluation threshold for leachables; based on the Product Quality Research Institute's (PQRI) Orally Inhaled and Nasal Drug Products (OINDP) recommendations

USP Guidance on Extractable and Leachable

The control of drug product leachable starts with the selection and control of packaging materials and components.

- Plastic
  - <661.1> Plastic Materials of Const ruction
  - <661.2> Plastic Packaging System for Pharmaceutical Use
  - <665> Plastic Component and Systems Used in the Manufacturing of a Drug Product (*PF 45(2)*)
- Elastomeric Component Used for Pharmaceutical Use
  - <381> Injectable Drug Products
- *USP* <660> *Glass Containers Used for Pharmaceutical Use*
- *USP* <662> *Metal Containers Used for Pharmaceutical Use* Biocompatibility Testing of Plastic and Elastomeric Material
  - <87> Biological Reactivity, In Vitro
  - <88> Biological Reactivity, In Vivo
  - <1031> Biocompatibility of Materials

Contents

Adulteration

Over the years, many countries around the world, including the United States have been challenged by economically motivated adulteration. Examples include:

- Diethylene glycol in glycerin
- Oversulfated chondroitin sulfate in heparin
- Melamine in pet food and infant formula

Such instances involve the deliberate substitution of a less costly substance for a more expensive one, resulting in patient harm and even death.

Diethyleneglycol and Ethylene Glycol in Glycerin and Related Excipients

- Fatal Poisoning reported among Young Children due to contaminated Acetaminophen oral syrups --- Nigeria, 2008—2009
- Glycerin used as a sweetener in oral syrup formulations
- Diethyleneglycol (DEG) (and ethylene glycol and propylene glycol) - contaminated glycerin was used in the oral syrup preparations
- DEG is a nephrotoxin and hepatotoxin and is used in industrial solvents and antifreeze
- USP monograph revised to include.
  - A GC Limit of diethylene glycol and ethylene glycol added to the Glycerin, Propylene Glycol and Sorbitol solution monographs

Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 45, 649 (1996) C. M. Gryniewicz et al, Amer. Pharm. Review 10 (7) 24 (2007) W. Bogdanich and J. Hooker, "From China to Panama, a Trail of Poisoned Medicine, The New York Times, May 18, 2007

Heparin Adulteration

- In 2007-2008, serious injuries and deaths were associated with the use of heparin.
- In February 2008, Baxter Healthcare Corporation recalled multi-dose and single-dose vials of heparin sodium for injection
- FDA scientists together with USP identified a contaminant, oversulfated chondroitin sulfate (OSCS), in the heparin (nuclear magnetic resonance, capillary electrophoresis, enzymatic kinetics, and bioassay).
- OSCS mimics the biological activity of heparin
- Source identified to be API manufactured in China
- USP revised monographs for heparin sodium and heparin calcium, to quantitatively measure OSCS

Melamine Adulteration

- Granular melamine was found (2008) to have been intentionally added to product formulations, including infant formula, in order to pass protein tests by indicating a higher level of protein than actually existed in the products.

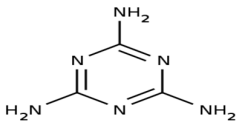
  EXAMPLES OF AT-RISK PHARMACEUTICAL COMPONENTS (e.g., Urea)

Guidance for Industry "Pharmaceutical Components at Risk for Melamine Contamination"
Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM) August 2009

Melamine Adulteration

Protein Content by Nitrogen Determination, Method II <461>

Melamine



Contents

Impurities in Water and Excipients

- Water
  - Inorganic impurities: Cl^-, $SO4^{2-}$, $NO3^-$, Hypochlorite (OCl^-), Ca^{2+}, Na^+, K^+
  - Organic impurities: Phenols, Chlorobenzene, Ethylbenzene, Toluene, Xylenes, Chloramines
  - Endotoxins
- Excipients:
  - Elemental impurities - As
  - Inorganic salts – Ca, Mg, Al
  - Organic impurities

Impurities in Water Pharmaceutical Purposes

- Organic Impurities:
  - Bulk Waters: Limited by a Total Organic Carbon (TOC) test
  - Sterile Packaged Waters: Limited by an Oxidizable Substance test (In process to be changed to a TOC test with variable limit based on container size)
- Inorganic Impurities:
  - Limited by a Conductivity test

Elemental Impurities in Water Pharmaceutical Purposes

- A revision to chapter <1231> proposed in *PF* 43(2) [Mar-Apr, 2017] became official in the *First Supplement to USP 41-NF 36*
- It included new proposed section, 7.4., intended to provide clarification about compliance with elemental impurities requirements in compendial waters
- According to compendial considerations, it is concluded that, if the feed water complies with US EPA NPDWR or the WHO guidelines for the quality of drinking water for elemental impurities, the chemical purification technologies necessary to produce bulk or sterile waters that reduce impurities in a factor of 100 to 1000 will ensure compliance with chapter <232>, provided there are no elemental impurities added during processing, packaging, administration or storage

Impurities in Excipients

- Stimuli article published in *PF* 44(3) [May-Jun, 2018]:

"The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities":

- Nominal Component
- Minor Component
- Simple Excipient
- Complex Excipient
- Concomitant Component
- Added Substances in official articles
- Excipient Impurity

Discussion

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Contacting USP

Questions on Monographs that are already official:

Stdsmonographs@usp.org

Questions on Proposals for new monographs or revisions or General Chapters:

Scientific Liaison (name is given in PF at the end the proposal)

Reference Stds Questions:

RSTech@usp.org

Thank You

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